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Journal of Pharmaceutical and Biological Sciences

Journal homepage: https://www.jpbs.in/

Review Article

A systematic review of potential anticancer activities of Muntingia calabura L. With a focus on cellular and molecular mechanisms

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Abstract

Medicinal plants have been extensively explored for their chemopreventive and antiproliferative properties. Among these, Muntingia calabura has emerged as a promising candidate due to its ability to modulate various signaling pathways involved in cancer progression and suppression. This includes interactions with multiple cell signaling molecules that regulate cancer formation and development. This review aims to critically evaluate the anticancer properties of M. calabura across different cancer types. A systematic literature search was performed across major scientific databases, including ScienceDirect, PubMed, and Scopus. Studies were selected based on predefined inclusion criteria using the keywords "Muntingia calabura", "M. calabura", "anticancer" and "cancer." A total of 13 studies met the eligibility criteria and were analyzed for this review. Evidence from the reviewed studies highlights the anticancer effects of M. calabura extracts, which include inhibition of inflammatory and apoptotic pathways. The modulation of dysregulated signaling cascades, such as the LOX, XO, and RAF1 pathways, was shown to contribute significantly to its anticancer activity. The findings support the potential application of M. calabura and its phytochemical constituents in cancer prevention and therapy. However, further in-depth studies are necessary to identify its bioactive compounds and elucidate the mechanisms underlying its anticancer effects for clinical translation.

Keywords: Muntingia calabura, Anticancer, Phytochemicals, Flavonoids

Received: 14-03-2025; **Accepted:** 06-05-2025; **Available Online**: 09-06-2025

1. Introduction

Medicinal plants have long played a significant role in treating various human diseases, including cancer. Several plant-derived compounds, such as Vincristine, Vinblastine, and Paclitaxel, have been successfully developed into anticancer drugs.[1-2] A major challenge in cancer therapy is to develop treatments that selectively target cancer cells while minimizing harm to healthy tissues and reducing drug resistance.[3] The use of plant-based compounds as alternative anticancer agents has gained increasing interest, with *Muntingia calabura L.* (Jamaican cherry) emerging as a potential candidate.[4-5]

M. calabura, the only species in its genus within the Elaeocarpaceae family, is a fast-growing tree native to tropical America and widely cultivated in Southeast Asia, including Malaysia, Indonesia, and the Philippines.[6] In Malaysia, *M. calabura*, locally known as "Kerkup siam", is commonly cultivated as a roadside tree.[7] The tree typically grows between 7.5 and 12 meters in height, with horizontally spreading branches, serrated leaves, small white flowers, and spherical fruits that ripen from green to red (**Figure 1**).[8-9] Various parts of the plant, including the leaves, stems, fruits, and roots, have been traditionally used to treat ailments such as headaches, fever, stomach pain, and liver infections.[10-12] Additionally, the fruits, leaves, roots, and bark of *M. calabura* have demonstrated pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, gastroprotective, and hepatoprotective effects.[13-15]

M. calabura is a rich source of essential macronutrients, including carbohydrates, proteins, and lipids, as well as micronutrients such as calcium, iron, and phosphorus.[16] More importantly, it contains a variety of bioactive compounds, particularly flavonoids (e.g., quercetin, kaempferol),

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DOI: https://doi.org/10.18231/j.jpbs.2025.004

phenolic acids (e.g., gallic acid, ferulic acid), tannins (e.g., ellagic acid), and triterpenoids (e.g., ursolic acid, oleanolic acid).[17-21] These compounds, predominantly concentrated in the leaves, exhibit significant antioxidant, anti-inflammatory, antimicrobial, and anticancer properties.[22-24]

Several studies have investigated the safety profile of M. calabura extracts. Acute toxicity studies in animal models indicate that oral administration of the plant's methanol and ethanol extracts is well tolerated at doses up to 5000 mg/kg, with no observed toxic effects.[25] Additionally, no signs of toxicity or mortality were reported in rats treated with ethanol and crude extracts at doses as high as 15,000 mg/kg.[26].

Further evidence from a 90-day sub-chronic toxicity study demonstrated no significant adverse effects in rats receiving methanol extracts at doses of 50, 250, and 500 mg/kg.[27] Histopathological, hematological, and biochemical analyses confirmed that M. calabura extracts do not disrupt normal physiological functions. These findings suggest that M. calabura is generally safe for consumption, reinforcing its potential as a therapeutic agent.

Despite its diverse medicinal applications, there is a lack of comprehensive reviews assessing *M. calabura's* potential as an anticancer agent. This review aims to systematically examine the available evidence on its anticancer properties and underlying mechanisms.

2. Materials and Methods

The present systematic review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[28] [Studies were selected from multiple electronic databases (Scopus, PubMed, Science Direct, Google Scholar, and EBSCO) up to July 2023. The search strategy employed the keywords: '*Muntingia calabura*' AND '*M. calabura*' AND 'cancer' AND 'anticancer' AND '*in vivo*' AND '*in vitro'*.

Inclusion criteria focused on experimental research both *in vivo* and *in vitro*, evaluating the anticancer potential of *M. calabura* in any animal model and/or cancer cell line. Unrelated papers were excluded based on titles and abstracts, with two independent researchers conducting the review to minimize bias. Review papers, meta-analyses, book chapters, conference abstracts, clinical trials, and non-English language materials were excluded. In total, 57 reports were excluded due to duplicate findings, 27 due to article type, and 10 for being review articles, leaving 50 studies. From these, 33 were eliminated for focusing on other pharmacological effects, and 5 for addressing phytochemicals not derived from *M. calabura*. Ultimately, 13 research papers were included, as depicted in the flowchart (**Figure 2**).

3. Results and Discussion

Out of the final 13 articles, 10 focused on in-vitro studies using cancer cell lines, while the remaining three utilized in-vivo animal models. The following section summarizes the anticancer properties of M. calabura, as outlined in (**Table 1** and **Table 2**)

The earliest in vitro study (1991) assessed 12 flavonoids from *M. calabura* roots for cytotoxicity against P-388 cells and selectivity towards eight human cancer cell lines. Flavans (compounds 1–7) exhibited stronger cytotoxic activity than flavones (compounds 8, 10, and 12), with ED_{50} values ranging from 2–16.7 µg/mL against BC1, HT-1080, Lul, Me12, Col2, KB, KB-V, and P-388.[29] Several compounds demonstrated selective activity against Me12 and KB cells, while compounds 3, 9, and 11 showed broader toxicity. A follow-up study confirmed that 2',4'-dihydroxychalcone and chrysin displayed significant cytotoxicity against multiple cancer cell lines (ED_{50}: 0.7–20 µg/mL), while galangin 3,7-dimethyl ether was selective for P-388 cells.[30] These findings highlight the potential of *M. calabura* flavonoids in anticancer drug discovery. Furthermore, flavonoid extracted from *M. calabura* leaves demonstrated chemopreventive activity, with an IC_{50} values exceeding 20 µg/mL against mouse Hepa 1c1c7 cells. This suggests that the compounds isolated from *M. calabura* provide a protective effect by mitigating the toxic impact of Quinone reductase.[31]

Table 1: Potential anticancer properties and related mechanism of action of *M. calabura* based on *in vitro* stud.

Reference	Cancer type	Cell line	lant part	Dose and duration	Anticancer effects	Mechanisms
Kaneda et al.[29]	Various	BC-1, HT-1080, Lul, Me12, CO12, KB, KB-V, and P-338	Root	20.0, 4.0, 0.8, 0.16, and 0.032 µg/mL	↑Cytotoxicity effect	NR
Nshimo et al.[30]	Various	BC-1, CO12, HT-1080KB, KB-V1, Lul, Me12, and P-388	Stem and leaves	NR	↑Cytotoxicity effect	NR
Su et al.[31])	Liver	Hepa 1c1c7	Leaves	NR	↑Quinone reductase ↑Cytotoxicity effect	NR

Chen et al.[32]	Various	P-388, a549, and HT-29	Leaves	NR	↑Cytotoxicity effect	NR
Chen et al.[33]	Colon	HT-29 and P-388	Leaves	NR	↑Cytotoxicity effect	NR
Zakaria et al.[34]	Various	3T3, MCF-7, HeLa, HT-29, HL-60, K-562, and MDA-MB-231	Leaves	100-12.5 µg/mL for 72 hours	↑Cytotoxicity effect ↑Antiprolifera-tive effect	↑ROS
Sufian et al.[35]	Various	MCF-7, HL60, HCT116, and WRL68	Leaves	0.01 to 100 mg/mL for 72 hours	↑Cytotoxicity effect	NR
Zakaria et al.[36]	Colon	HT-29	Leaves	30, 60 and 90 µg/mL for 72 hours	↑Antioxidant activity ↑Antiproliferative activity ↑Anti-inflammatory activity	↓OX/LOX
Lin et al.[37]	Liver	HepG2	Fruit	25, 50 or 100 µg/mL	↓Cell viability	↓VEGF ↓RAF1/MEK1/2/ERK1/2, and JAK2/STAT3 ↓PI3K/AKT/mTOR
Kumar et al.[38]	Laryngeal	Hep2	Fruit	20, 50, 70, and 100 µg/mL for 24 hours	↑Cytotoxicity effect ↑Apoptosis effect ↓Cell proliferation	↑G2 phase arrest

Notes: The symbols "↑" and "↓" represent an increase and decrease in specific anticancer activities, respectively. "NR" stand for not reported. VEGF: Vascular endothelial growth factor; 3T3: Normal mouse fibroblast; MCF-7: Oestrogen-dependent human breast adenocarcinoma; HeLa: Human cervical adenocarcinoma; HT-29: Human colon cancer; HL-60: Acute promyelocytic leukaemia; K-562: Chronic myelogenous leukaemia; MDA-MB-231: Human breast carcinoma; HepG2: Hepatocellular carcinoma; RAF1: Serine/threonine kinase; MEK1/2: Mitogen-activated protein kinase ½; ERK1/2: Extracellular signal-regulated kinase ½; JAK2: Janus kinase 2; STAT3: Signal transducers and activators of transcription 3; ROS: Reactive oxygen species.

Table 2. Potential anticancer properties and related mechanisms of action of *M. calabura* based on *in vivo* studies.

Reference	**Cancer type**	**Animal model**	**Plant part**	**Dose and duration**	**Anticancer effects**	**Mechanisms**
Nasir et al. [39]	Colorectal	Male Sprague-Dawley rats	Leaves	50, 250, and 500 mg/kg for 8 weeks	↓ACF number ↓Oxidative activity ↑Antioxidant activity	↑SOD, CAT, and GSH ↓MDA
Jisha et al.[40]	Colorectal	Female Wistar rats	Leaves	20 and 50 mg/kg for 15 weeks	↑Apoptosis effect ↓Cell proliferation ↑Antioxidant activity	↓NF-κB and COX-2 ↑SOD, CAT, & GR ↓MDA and ROS ↑RBC, Hb, and Hct ↓WBC ↓AST, ALT, ALP, and total bilirubin ↑Connexin-43, p53, Caspases-3, and Caspase-9
Jisha et al.[41]	Colorectal	Female Wistar rats	Leaves	100 and 200 mg/kg for 15 weeks	↑Antioxidant activity	↑SOD, CAT, and GR ↓MDA and ROS ↑Hb ↓WBC &ESR ↓AST, ALT, ALP and total bilirubin

Notes: The symbols "↑" and "↓" represent an increase and decrease in specific anticancer activities, respectively. SOD: Superoxide dismutase; CAT: Catalase; GSH: Glutathione; GR: Glutathione reductase; MDA: Malondialdehyde; ACF: Aberrant crypt foci; Hb: Hemoglobin; WBC: White blood cell; ESR: Erythrocyte sedimentation rate; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; NF-KB: Nuclear factor kappa B; COX-2: Cyclooxygenase-2.

Figure 1: The various parts of *M. calabura*. (a) The *M. calabura* tree. (b) The leaves of *M. calabura*. (c) The flower of *M. calabura*. (d) The fruit of *M. calabura* (Adapted from NParks, 2024).

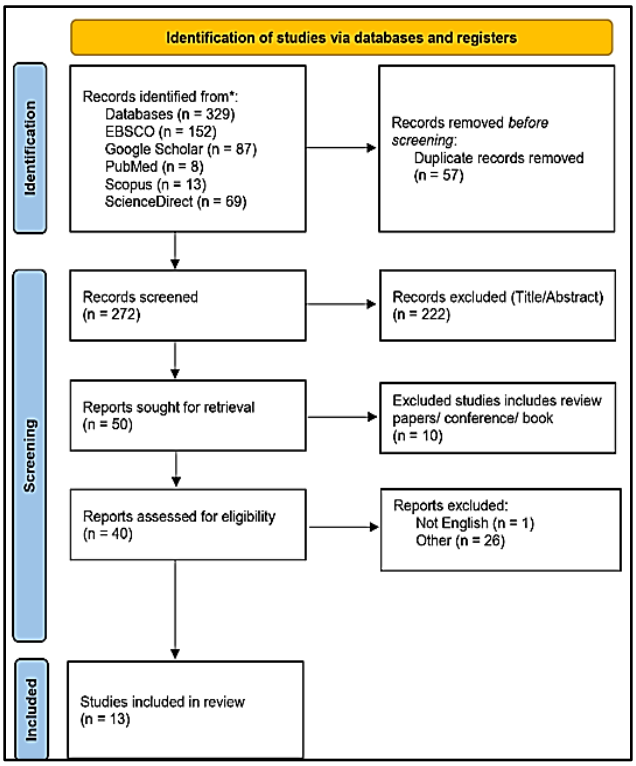

Figure 2: The flow chart of the PRISMA selection procedure for the included studies.

Subsequent research expanded cytotoxicity testing to P-388, A549, and HT-29 cells. Among the 15 isolated compounds, seven compounds (8-hydroxy-7, 3', 4', 5'-tetramethoxyflavone (1), 8, 4'-dihydroxy-7, 3', 5'-trimethoxyflavone (2), 3, 5-Dihydroxy-6, 7-dimethoxyflavone (5), (2S)-5'-Hydroxy-7, 8, 3', 4'-tetramethoxyflavan (6), Syringic acid (10), Vanillic acid (11), and 3-hydroxy-1-(3, 5-dimethoxy-4-hydroxyphenyl) propan-1 (12)) demonstrated cytotoxic activity against P-388 cells (ED_{50}: 3.27–15.62 µg/mL), while only one compound showed significant effects on HT-29 and A549 cells.[32] Further analysis of 20 isolates identified four flavonoids ((2S)-5'-hydroxy-7, 3',4'-trimethoxyflavanone, 4'-hydroxy-7-methoxyflavanone, 2',4'-dihydroxychalcone, and 2',4'-dihydroxy-3'-methoxychalcone) with notable cytotoxicity (IC_{50} <4 µg/mL) against P-388 and/or HT-29 cells.[33]

In another study, the antiproliferative activity of chloroform, aqueous, and methanol extracts of *M. calabura* was tested against MCF-7, HeLa, HL-60, K-562, MDA-MB-231, and 3T3 cells using the MTT assay (12.5–100 µg/mL) [34]. None of the extracts inhibited MDA-MB-231 or 3T3 cell proliferation, suggesting selective cytotoxicity towards cancer cells. The aqueous, methanol, and chloroform extracts exhibited antiproliferative effects against MCF-7 (IC_{50}: 18–98 µg/mL), HeLa (IC_{50}: 23–52 µg/mL), K-562 (IC_{50}: 18–42 µg/mL), HT-29 (IC_{50}: 16–46 µg/mL), and HL-60 (IC_{50}: 7–29 µg/mL). These effects are likely due to the plant's antioxidant properties and high polyphenolic content, with methanol extracts showing the strongest antioxidant activity.

A study on the cytotoxicity of *M. calabura* methanolic (MeOH) extract and its partitions (petroleum ether (PEE), ethyl acetate (EAE), and aqueous (AE)) against MCF-7, HL-60, HCT116, and WRL68 found that MeOH showed moderate cytotoxicity against HL-60 and HCT116 (IC_{50}: 30.90 and 61.29 µg/mL, respectively) [35]. PEE and EAE exhibited IC_{50} values of 29.46 and 47.19 µg/mL (PEE) and 17.26 and 58.44 µg/mL (EAE). None of the partitions showed substantial cytotoxicity against MCF-7, and AE lacked cytotoxicity against all tested cell lines (IC_{50} >100 µg/mL). EAE demonstrated selectivity toward HL-60 (SI=4.54) compared to WRL68, suggesting its potential in cancer therapy. Further fractionation of EAE identified 7 major fractions, of which F5 was the most active (IC_{50}: 3.98, 34.85, and 32.29 µg/mL for HL60, MCF7, and WRL68). Four bioactive compounds were isolated, including two novel flavones (5,7-dihydroxy-3,8-dimethoxyflavone and 5-hydroxy-3,7-dimethoxyflavone). The other 2 Compounds have been reported previously to possess various biological activities such as antimicrobial, cytotoxicity, antioxidant, and anti-inflammatory activity.

The ethyl acetate partition (EAP) showed potent antiproliferative activity against HT-29 (IC_{50}: 58 µg/mL) while sparing normal 3T3 cells. It also exhibited high inhibition of LOX (>95%) and XO (>70%), indicating anti-inflammatory potential[36]

M. calabura fruit ethanolic extract (MFEE) reduced the vascular endothelial growth factor (VEGF) expression in nickel-stimulated HepG2 cells in a dose-dependent manner, resembling the effect of gallic acid.[37] MFEE also downregulated RAF1, MEK1/2, ERK1/2, PI3K, JAK2, STAT3, AKT, and mTOR while sparing P-38 and P-JNK1/2 expression, highlighting its anticancer potential. This was strengthened by the similar result presented by gallic acid, the major phenolic compound in MFEE, which was used for comparison. VEGF plays a crucial role in cancer promotion and angiogenesis, therefore, the down-regulation of VEGF

expression and the reduction of neovascularization is one of the target effects of cancer treatment.

Gold nanoparticles synthesized with *M. calabura* extract (MC-AuNPs) selectively induced apoptosis in Hep2 cells, causing membrane disruption, nuclear alteration, and G2-phase cell cycle arrest.[38]

Transitioning from *in vitro* to *in vivo* investigations, the chemopreventive potential of *M. calabura* against colon cancer in rats was explored. The study showed a reduction in aberrant crypt foci (ACF) formation, indicating a potential role for *M. calabura* extracts in protecting against colon carcinogenesis.[39] The reduction in ACF number is attributed to the antioxidant activity of MEMC. The findings showed that MEMC treatment increased antioxidants levels such as SOD, CAT, and GSH while decreasing the level of oxidative stress markers like MDA in the colon tissues of rats. Additionally, HPLC analysis of MEMC identified various phenolic compounds, including gallic acid, catechin, epicatechin, ferulic acid, and pinocembrin, which are known to possess antioxidant, anti-inflammatory, and anticancer properties.

Similarly, the anticancer effects of the ethyl-acetate fraction of *M. calabura* (EFMC) revealed improvements in antioxidant levels, modulation of inflammatory markers, and regulation of apoptotic genes. These changes may be attributed to its inhibition of the NF-κB pathway, which plays a crucial role in CRC development.[40-41] Additionally, EFMC was found to downregulate the expression of genes such as COX-2, TNF-α, p53, IL-6, Casp-9, Casp-3 and Connex-43, all of which are involved in CRC development. RT-PCR analysis revealed that DMH treatment downregulated Connexin-43, Caspases-3, p53 and Caspase-9 gene expression, while EFMC significantly increased expressions. These findings were supported by western blot analysis, which showed increased expression of COX-2 and NF-κB in the DMH group, while EFMC treatment caused a significant reduction in the expression of COX-2 and NF-κB.

Overall, the ant proliferative and cytotoxic properties of *M. calabura* extracts, compounds, and partitions against various cancer cells are primarily attributed to their rich phytochemical composition. Studies have identified bioactive constituents, including phenolic acids and flavonoids, which likely act synergistically to exert anticancer effects.

4. Conclusion

In conclusion, the collective findings from *in vitro* and *in vivo* studies underscore the potential of *Muntingia calabura* as a promising source of anticancer agents. This review highlights its selective cytotoxicity against multiple cancer cell lines and its chemopreventive effects in animal models. Given its affordability, long history of use, widespread availability, and diverse pharmacological activities, *M. calabura* holds promise as an anticancer and chemopreventive agent. Studies have demonstrated its effects against a range of cancers, including breast, colon, laryngeal, lung, prostate, hepatocellular carcinoma, melanoma, and leukemia, with potential applications beyond these types.

The observed selective cytotoxicity, alongside its modulation of critical cellular pathways such as NF-κB/IL-6/STAT3, IKK/NF-κB, PI3K/Akt/mTOR, ERK, Bcl-2, and VEGF, suggests that *M. calabura* could play a significant role in future anticancer strategies. However, since most existing evidence is derived from *in vitro* studies, with limited *in vivo* or clinical data, further research involving animal models and randomized clinical trials is crucial. To fully harness its therapeutic potential for cancer treatment and prevention, deeper investigations into its mechanisms and clinical applications are essential.

5. Acknowledgement

This work was supported by the Fundamental Research Grant Scheme [FRGS/1/2018/SKK10/UPM/02/4] and the Geran Putra Berimpak [UPM/800-3/3/1/GPB/2020/9685000].

6. Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Cite this article: Alseaghi MH, Khalid M, Ali RM, Hakim MZ, Zakaria ZA. A systematic review of potential anticancer activities of Muntingia calabura L. With a focus on cellular and molecular mechanisms. *Jaurnal of Pharmaceutical Biological Science.* 2025;13(1):20-25.